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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,989	DAVIS, PETER DAVID	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10,13,14,21 and 24-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10,13,14,21 and 24-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 4-10, 13, 14, 17, 19- 21, 24, and 25 are pending and examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

This Office action contains new grounds of rejection.

Claim Objections

Claims 33 and 37 are objected to because of the following informalities: claim 33, line 2 says "ad administration", and claim 37, line 1 says "acc according". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

Claim 1 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bonfoco et al (1995, Experimental Cell Research, vol. 218, pages 189-200).

The claim is interpreted as drawn to a composition comprising a tubulin binding agent and an NO synthase inhibitor.

Applicant argues that Bonfoco et al., do not disclose a pharmaceutical composition according to the present invention. In Bonofoco et al., colchicine is along with NO synthase inhibitors such as NMMA or others on the cell damage induced by

colchicines exposure, colchicines and NMNA together in Table 1 of the art is in the cell culture medium containing the rat cells, cell culture medium containing the rat cells is not a pharmaceutically acceptable excipient. The cell culture medium and rat cells in which the colchine and NMMA are present in Bonfoco et al., could in no way be described as a pharmaceutically acceptable excipient as required by the present claims.

These arguments have been fully considered but found unpersuasive because Bonfoco et al., teach composition comprising colchicines (a tubulin binding agent) and NMMA (an NO synthase inhibitor) at Table 2, 1st column, row 6. The specification at page 3 lines 8-23 "The vascular damaging agent and the nitric oxide synthase inhibitor can be administered by the same route or by different routes" and "Each component of the method, the vascular damaging agent and the nitric oxide synthase inhibitor may independently be administered in a form suitable for the intended route of administration and such forms may be prepared in a conventional manner using conventional excipients", fairly suggests that instant pharmaceutical composition does not have be mixed together in **a single vial** with a single pharmaceutical excipient. When each component is individually administered in the case of Bonfoco et al., to the cell culture, they are composition. Further, the composition of Bonfoco et al., appears to be in a pharmaceutically acceptable excipient because Bonfoco et al., at page 190 under MATERIALS AND METHODS, sub-heading "Materials" teach that all of the reagents including colchicines and NMMA from Sigma were prepared as stocks in PBS.

Claim Rejections - 35 USC § 103

Claims 2, 4-10, 13, 14, 21, 24, and 25 **remain rejected** and the **new claims 26, 27, 31, 33, 34, 35, 36, 37, 38, 39, 40, 43, 44, 45, 46, 48 are also rejected** under 35 U.S.C. 103(a) as being unpatentable over Chaplin et al (1998, a copy provided with ISR, Seminars in Radiation Oncology, vol. 8, pages 151-163).

The claims are interpreted as drawn to composition comprising two genuses, i.e. a tubulin binding agent and an NO synthase inhibiot with the specific agents belong to the two genuses recited in the dependent claims, and method of using said composition for inhibiting unwanted angiogenesis and treating cancer.

Applicant argues that the NO synthase inhibitors and vascular damaging agents described in Chaplin et al are not described therein as having the same purpose at all. Chaplin et al that the mode of action of the NO synthase inhibitors and vascular targeting agents is not the same and as such the In re Kerkhoven analysis applied, by the Examiner is not appropriate. In Kerkhoven, the issue before the court was the obviousness of a procedure in which two conventional spray dried detergents were mixed together. It was claimed that the resulting mixture would have good free-flow properties. The court concluded that " it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose." The court was not satisfied that there was sufficient evidence of superiority for the claimed product to overcome the prima facie case.

These arguments have been fully considered but found unpersuasive because Chaplin et al teach the various recited agents belonging to the two genuses are known

in the art and had been used in inhibiting unwanted angiogenesis and/or tumor blood flow. Applicant attention is directed at the title. Chaplin et al., are a review of the state of art in cancer treatment by tweaking blood flow to tumor cells no matter what the mechanism of the actions of each of the two genuses are. Chaplin et al., clearly teach both compounds belong to the two genuses have been recognized as therapeutic value for cancer treatment by limiting tumor blood flow.

Applicant argues that the specification at Example 1, Tables 1-3 show the combination exhibits "a surprising antitumor effect" and the effect of the combination is far greater than the use of either agent alone. These arguments are fully considered but not persuasive because the unobviousness argument based on the unexpected result should be in commensurate in scope. The specification at Example 1, Tables 1 and 3 are limited to a specific combination CA4P and L-NNA, while the Table 2 is limited to the specific combination of CA4P with AMP. However, the claims are broadly drawn to any composition between the two genuses.

The instant claims can be viewed as a composition and methods drawn to administering a combination of ingredients known in the art to be useful for the same purpose, i.e. an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the

time the invention was made to combine a tubulin binding agent and a NO synthase inhibitor known to be useful for the treatment of inhibiting angiogenesis and/or limiting blood flow to tumor because the prior art teaches useful for treating cancer.

The Following are New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 is written in the form of alternative expression commonly known as Markush groups. However, Claim 37 is confusing. The first member of member i.e. "N^G-nitro-L-arginine" is about what is substituted at N^G position of N^G-substituted L-arginine but the some other members do not. Note MPEP2173.05(h). Does "N^G or N^G ino-L-arginine belong to a member of "nitric oxide synthase"? How is "alkyl esters thereof" related to other members of Markush groups?

Claim 38 recites the limitation "the derivative" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 39 recites the limitation "the derivative" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 40 recites the limitation "the derivative" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

Claims 1, 2, 28, 13, 33, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaplin et al (1998, a copy provided with ISR, Seminars in Radiation Oncology, vol. 8, pages 151-163) in view of Ohsumi et al., J Med Chem. 1998 Jul 30;41(16):3022-32.

Claims 1, 2, 13, 28, 33, and 47 are interpreted as drawn to pharmaceutical comprising an NO synthase inhibitor and **(Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine** and method of treating cancer using said pharmaceutical.

Chaplin et al teach that an NO synthase inhibitor and tubulin binding agents have been used in the art for treating cancer.

Chaplin et al do not teach (Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine.

However, Ohsumi et al., teach that (Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine (note page 3030) is an analog of combretastin A-4 that has been effective in treating cancers, and the analog is also expected to have a action similar to combretastin A-4 disclosed by Chaplin et al.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make and use (Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine for combination treatment with an NO synthase inhibitors for cancer treatment and/or as pharmaceutical with reasonable expectation of

success since Chaplin et al., along with Oshumi et al., teach how to make and use each elements in the claims.

Claims 2, 29, 30, 32, 35, 41, 42, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaplin et al (1998, a copy provided with ISR, Seminars in Radiation Oncology, vol. 8, pages 151-163) in view of WO 96/18617 (IDS, AO).

The claims are interpreted as drawn to pharmaceutical comprising an NO synthase inhibitor listed in the each of the claims in combination of a tulin binding agent for treating caner.

See what Chaplin et al teach above. Chaplin et al do not list the specific NO synthase inhibitors.

However, WO 96/18617 list all of the compounds listed in the instant claims.

Since the instant specification does not disclose any new compound, but discloses specific combination of art known compounds have synergy, and the compounds listed in the claims are not those listed at Table 1 and 2 of the instant specification, and WO 96/18617 teach various specifically recited NO synthase inhibitors have been used in as an pharmaceutical for cancer or other disease treatment, combining two known compounds useful for cancer treatment is obvious.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
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LARRY R. HELMS, PH.D
PRIMARY EXAMINER